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UNIVERSAL HPV VACCINATION – A GLOBAL PREROGATIVE

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ABSTRACT

Worldwide cancer incidence is increasing, with viral infections including human papillomavirus (HPV) responsible for a significantly higher number of cancer deaths in low- and middle-income countries (LMICs) when compared to high income countries. Globally, in 2015, there were 72 national HPV vaccination programmes, and 39 demonstration or pilot programmes. Despite HPV's impact on both sexes, for examples in malignancies such as oropharyngeal cancer (whose incidence is increasing across the world) few countries have a gender-neutral vaccination policy. Herd protection and cost-effectiveness are important considerations in potential extension of vaccination to males and while there is some suggestion that a targeted vaccination programmes for "high risk" groups, such as men-who-have-sex-with-men (MSM) may be preferable, a universal vaccination approach is the best solution to protect both men and women from HPV-related cancer and sexually transmitted disease. Higher incidence of certain HPV-related male cancers, lack of effective treatment, high prevalence of HIV, attitudes to MSM and sexual orientation, all support a universal vaccination strategy for LMICs. Thus, policy-makers and healthcare providers in LMICs need to take timely decisions to "prevent the preventable" by providing vaccination for both girls and boys.

There is a global gender difference in cancer incidence and mortality, with the burden in men being much higher than in women, in 2012, there were 126 cancer deaths per 100 000 men, and 83 for every 100 000 females.^{1,2} Cancer incidence is increasing, with more than 60% of new cases occurring in Africa, Asia, and Central/South America, and two thirds of all cancer deaths occurring in the developing world.³ This burden can be partly explained by limited primary and secondary preventative strategies and poor availability of detection and treatment methods.⁴ Significant cancer health disparities are evident, both across and within countries, including race and/or ethnicity, and avoidable inequalities, such as socioeconomic status and sexual activity.^{5,6} It is this last factor – sexual activity and its link to sexually transmitted disease and cancer – which will be the focus of this perspective piece.

VIRUSES AND CANCER: THE ROLE OF HUMAN PAPILLOMAVIRUS

Viral infections, including Human Papillomavirus (HPV), are responsible for approximately 15% of all cancers worldwide, with low middle-income countries (LMICs) reporting much higher prevalence (e.g., 33% in sub-Saharan Africa).⁵ These infections lead to one fifth of cancer deaths in LMICs.⁷ HPV is the most common of all infections leading to cancer and hence is a crucial determinant of a significant global cancer burden; thus it demands the effective implementation of preventative or curative interventions.⁸

Globally, HPV is one of the most common sexually transmitted infections; there are numerous types of HPV, and varying degrees of risk linked with continual infection from each type. Many infections are short-lived and clinically unimportant, but repeated infection with particular strains of HPV causes a considerable burden

of disease in both men and women. HPV prevalence in men has been reported to be consistently higher than in females, due to a poorer natural immune response to HPV in men compared to women.⁹

Of the estimated 12.7 million cancers globally, 610 000 were attributed to HPV infection.¹⁰ In women, cervical cancer has been linked to HPV, with only a small fraction being HPV-negative.¹¹ More than 40,000 of these cases occurred in men.¹² Furthermore, in the future, males are predicted to have a greatly increasing incidence of anal, penile and oropharyngeal cancers.^{8,13} In countries with limited screening, mortality from cervical cancer far exceeds that of HPV-related disease in men; however, in the developed world, HPV cancer in men is similar to that of cervical cancer.^{14,15} However, unlike cervical cancer, there is no recommended screening programme for male HPV-related cancers.¹²

OROPHARYNGEAL CANCER

Oropharyngeal cancer (OPC) shows a regional variation/heterogeneity in prevalence; in comparison to the high-income areas of North America, Northwest Europe, Australia and Japan (41–51%), the rest of the world has a much lower prevalence (13–24%).¹⁶ The incidence of OPC is rising.¹⁷ Researchers have reported that men are twice as likely to develop HPV-OPC than women;¹⁸ in Canada in 2012 the incidence rate of HPV-OPC was more than 4.5 times higher in males than females.¹⁹ In the USA, it is predicted that the number of HPV-related OPCs diagnosed per year will soon surpass the annual number of cervical cancer cases.²⁰

PENILE CANCER

Although penile cancer is a rare disease, its incidence is higher in less developed countries, where it can account for approximately 10% of male cancers in parts of Africa, South America, and Asia.²¹ Around 25–33% of penile cancers have been linked to HPV.²²

ANAL CANCER

Anal cancer incidence has increased rapidly in recent years in both males and females.²³ In Africa, anal cancers present at a younger age and more advanced stage.²⁴ Crucial for male health, men-who-have-sex-with-men

(MSM), who are estimated to be 5% of men, are disproportionately more likely to develop anal cancer (15:1 compared with heterosexual men).¹⁴ These rates of HPV in males are similar to cervical cancer rates before the introduction of screening.²⁵ HPV infection in men may also increase the risk of acquiring HIV infection²⁶ as it potentially increases the permeability of the genital lining to HIV.²⁷ Accordingly, anal cancer incidence rates are significantly higher in HIV-positive men than HIV-negative (70–100 versus 35 per 100,000 person years).²⁸ This is a particular concern for LMICs who bear most of the burden of the global HIV epidemic.²⁹

OTHER HPV-RELATED DISEASES

In addition to cancer, infection with low-risk HPV strains (i.e., 6/11) is implicated in the development of anogenital warts (AGW).³⁰ AGW are a significant burden in both men and women. Incidence of AGW appears to be similar worldwide, although there is little reliable LMIC data available.¹⁰ Prevalence estimates suggest 160–289 per 100,000 with a peak in males between the ages of 25–29 years.³¹ HPV infection can also be transmitted to a foetus by a pregnant mother, which could lead to RRP.¹⁴ There is a low prevalence of RRP (1–4 per 100,000), but it carries a high economic burden.³²

Preventing HPV Associated Cancer: Vaccination Works

There is an effective solution to address the burden of HPV. Three HPV vaccines are licensed for use: a bivalent vaccine which protects against the two high risk HPV types (HPV16/18), a quadrivalent vaccine protecting against HPV 16/18, genital warts and RRP (by eliminating the maternal reservoir for HPV) (twHPV6/11); and a nonavalent vaccine that protects against nine of the most common virus types (HPV6/11/16/18/31/33/45/52/58). As the vaccine was initially approved for cervical cancer prevention in females, there are fewer studies of the vaccines' preventative effect in males.³³ However, the HPV vaccine has shown a good safety profile and efficacy in younger (aged 9 to 15)^{34–36} and older males (aged 16–26).^{9,37,38} Furthermore, immunogenicity of the nonavalent vaccine in males was shown to be similar to

that in same age females.¹⁴ Pinto et al., demonstrated that HPV antibodies in the oral cavity in males can be generated through vaccination, but it will take many years before the research will be able to ascertain the effectiveness of HPV vaccination on male cancer outcomes.³⁹

Vaccination in Men – Pros and Cons

Despite the impact of HPV on males, only 11 countries have implemented a funded universal HPV vaccination programme for both sexes. Crucially, coverage rates of these universal programmes are far from optimal, and range from 39.7% (USA) to over 80% (Canada).^{40,41}

Many countries that offer female-only vaccination programmes defend this decision based on the rationale that males will be protected as a result of herd protection.⁴² Many countries may not view HPV vaccination as a male issue, which may be particularly pertinent for LMICs, due to the huge cervical cancer burden in these countries. The incremental benefit of extending the vaccine to males is widely believed to be highly dependent on coverage in females. However, a European study demonstrated that vaccination of 12-year-old boys and girls versus a high uptake “girls-only” vaccination would be associated with substantial additional clinical benefits in terms of reduced incidence of HPV-related genital warts and carcinomas.⁴³

Herd protection is feasible if females have high HPV vaccine uptake and males only have sexual contact with vaccinated females; however, sexual behaviour is not that simplistic. Sexual mixing must be considered. Unvaccinated males risk HPV infection due to sex with partners of the same sex, older partners, foreign partners (due to migration or growing international travel for leisure or business) and sex workers.⁴⁴

The major argument against implementation of universal vaccination has been the cost of this program, and a number of studies initially did not find universal vaccination cost effective.⁴⁵ However, there is mounting evidence that universal vaccination is cost-effective, at least in western populations,⁴⁶ particularly when the costs associated with OPC⁴⁷ and genital warts treatment⁴⁸ are considered, and the dose schedules are changed from 3 to 2 doses.⁴⁹ It has been proposed that considerations on the cost of universal

HPV vaccination should be expanded to encompass the broader economic consequences and benefits to society. When universal vaccination is approached from the perspective of a life-time cost-benefit analysis, wider economic benefits are demonstrated such as increased productivity, increased earnings and enhanced tax revenue.⁵⁰

From an ethical perspective, to “not fund” a vaccine for any group of individuals at risk of developing a vaccine-preventable disease is questionable; thus, including boys in vaccination campaigns is important to ensure equity in protection from HPV-related diseases.⁵¹ It is also unfair for females to be expected to bear the burden of HPV prevention through vaccination, particularly when HPV is a virus that is sexually transmitted, and affects both sexes so prolifically.^{15,52} With the burden of HPV-related disease in men in developed countries comparable to women, and no screening programme available in males for anal cancer or OPC, it is questionable to have a public health policy that is reliant on men being protected solely by herd immunity.¹⁵

Targeted Vaccination Towards “High Risk” Men

It has been suggested that the female-only vaccine programme be extended to “high-risk” men such as MSM who do not profit from female-only vaccination strategies or those men with HIV in an effort to balance protection versus cost.⁵³ Requiring the disclosure of sexual orientation as a prerequisite for vaccination could be seen as ethically questionable.¹⁵ It is impractical and unethical to ask adolescent boys if they are likely to have sex with another male when they are older, and if so, would they consider HPV vaccination.⁵⁴ In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) issued a recommendation that MSM up to age 45 years should be offered HPV vaccination via Genito-Urinary Medicine (GUM) and HIV clinics. A pilot programme is currently being undertaken in England. Superficially, this may seem to be a cost-effective solution, but a targeted MSM HPV vaccination programme may be difficult to implement, and may have limited efficacy in preventing HPV-related disease, as the HPV vaccine is thought to be most effective when given at a younger age (9–15 years), before exposure to HPV

through sexual contact and when immunogenicity is at its highest.⁵⁵ In addition, most MSM are likely to have delayed in their presentation to a HCP and to have had multiple sexual partners with increased risk of HPV acquisition before they attend a sexual health clinic.^{56,57} There is evidence that once they do attend a GUM clinic, the majority of MSM will re-attend within 24 months, which could facilitate the delivery of the HPV vaccine programme.⁵⁸ There are also MSM who do not identify as gay or homosexual and will not disclose their sexual activity to a HCP, meaning that they will never be offered the vaccination. The discriminatory impact of this policy would be amplified in countries where homosexuality is illegal, a considerable issue in LMICs.

Vaccination in LMICs – Current Situation and the Potential for Universal Vaccination

The greatest public health impact of HPV vaccination will be in countries where large portions of the population have limited or no access to secondary prevention cancer screening.⁵⁹ However, there is no consideration of universal vaccination in LMICs, in fact the WHO guidelines do not include HPV vaccination of boys.⁶⁰ HPV vaccine recommendation needs to be widened with consideration given to inclusion of adolescent males in vaccination programmes in LMICs.

Globally, HPV vaccination (routine use for adolescent girls) has only been introduced in 35% of countries.⁶¹ In August 2015 there were an estimated 72 national HPV vaccination programmes, and 39 smaller scale demonstration or pilot programmes.⁴⁰ The largest proportion of national programmes were in high-income countries in Europe, with LMICs having the most pilot programmes. There are still a large number of LMICs with no vaccination programmes.⁶²

According to the Program for Appropriate Technology in Health (PATH), since 2007, more than 1,625,000 girls in LMICs have participated in HPV vaccine programmes, with 800,000 completing a full vaccine schedule. Forty-one countries (84%) reported coverage of 70% or higher; no project or programme had coverage of less than <50% (in comparison to USA's 39.7% uptake). This high uptake suggests that if these programmes were extended, effective coverage of boys may also be achieved.

Understandably, cost is a considerable barrier to HPV vaccination programmes in LMICs. WHO determines a threshold for cost-effectiveness as the cost of the intervention per disability-adjusted life year averted as less than 3 times the per capita gross domestic product (GDP) of a country. However, concerns have been raised about the universal applicability of this strategy, and whether affordability is truly reflected in this figure.⁶³ By their nature, cost-effectiveness studies are applicable to the country from which the data was sourced. Studies in LMICs have largely focused on female vaccination for cervical cancer prevention. These studies are heterogeneous and some lack clarity regarding country-specific costs, including implementation of vaccination programs, and vaccine cost. However, overall the data supports cost-effectiveness, and potentially cost savings with the establishment of female vaccination programs, particularly where inadequate screening for cervical cancer is available.^{64,65}

The majority of studies incorporating male vaccination have focused on the developed world where vaccination costs are considerably higher. However, a Mexican study highlighted that a universal program with catch-up vaccination for both sexes would be the most effective strategy for prevention of HPV-related disease, but this optimal strategy increased cost per quality-adjusted life year (QALY) from approximately \$3000USD to \$16000USD.⁶⁶

To assist with costs in LMICs, a financing mechanism is available through GAVI, the Vaccine Alliance, or the Pan American Health Organization (PAHO) Revolving Fund for Latin America and Caribbean countries, both of which reduce the per-dose cost. GAVI subsidises introduction of HPV vaccination in LMICs, until countries can afford the vaccines. GAVI has negotiated a low price of approximately \$4.50 per dose (compared to \$100 for high income countries), with low-income countries paying only a small fraction of this as a co-payment.⁶⁷ The cost reductions supported by the GAVI alliance, would reduce expense for introduction of a universal vaccination program within LMICs. However, the actual reductions in vaccination delivery cost remain unclear and prevent accurate assessment of cost-effectiveness. This has been analysed by a number of LMIC pilot

projects, demonstrating that the differing methods of delivering the program, dependent on school attendance and population density, result in varying estimates of cost.⁶⁸ The complexities in incorporating financial factors when making a determination regarding optimal HPV vaccination strategies in LMICs have been acknowledged by WHO, with an expert group convening to address these issues.⁶⁹

Linking Health Interventions

Adolescents in LMICs face considerable health risks and health systems in these countries have difficulty ensuring access to appropriate cancer control measures. According to the WHO (2014),⁶⁰ there is an opportunity to link the delivery of the vaccine with other adolescent health interventions, including vision screening, information provision, and life skills development (e.g., physical activity; menstrual hygiene education, sexual health education; other vaccines) (WHO, 2014).⁶⁰ However, the introduction of HPV vaccination should not be delayed if other relevant health interventions cannot be introduced concurrently.⁶⁰ Additionally, HPV vaccination provides the opportunity to include health education that focuses on modifying behaviours that lead to HPV transmission, and an opportunity to inform and educate women on screening, diagnosis, and treatment of precancerous lesions and cancer.⁶⁰

Enhancement of HPV Vaccine Coverage

As has been discussed, many countries report low HPV vaccine uptake in males. In order to maximise benefit from vaccination, it is important to understand the factors that influence and enhance vaccine coverage.

A key question is whether or not men would accept vaccination if offered. Many countries' information campaigns are targeted to females-only, with a clear focus on cervical cancer. This connotation that HPV is a women's problem, and its subsequent impact on primary prevention efforts is referred to as the "feminisation of HPV."³³ This 'feminisation' is important as it impacts on how the general public, HCPs and policy makers view HPV and HPV vaccination as a female-only issue.³³ If existing programmes are to be extended to boys, better health education and public information campaigns must maximise public awareness that HPV should be of concern to both

sexes. However, knowledge is not always predictive of vaccine acceptance and uptake, with high uptake seen in populations with low knowledge.⁷⁰ A recent meta-analysis of 22 studies (8360 participants) reported a moderate level of acceptability among men (overall mean acceptability of 56.6%; range 8.2 – 94.0%), with no difference between MSM and heterosexual men. Factors associated with vaccine acceptability were positive HPV vaccine attitudes, healthcare professional (HCP) recommendations, perceived risk, HPV awareness and knowledge.⁷¹ For parents of adolescent boys, the perceived benefit of HPV vaccination in preventing cancer in males was found to be the most important predictor of vaccine acceptability.⁷²

Political will is essential for HPV vaccination programme implementation. New public health interventions, such as the HPV vaccine, demand more cost-effectiveness and sustainability evidence in order to convince policymakers.⁷³ For successful universal vaccination, it will be crucial to educate policy makers on the merit of including boys in HPV vaccination programmes. PATH/LSHTM's review⁷⁴ indicated that political support was fundamental to successful demonstration and introduction of pilot projects in LMICs.

There have been a number of studies testing the effectiveness of interventions to boost uptake. The majority have involved written information to educated populations, which limits their generalizability, while low uptake groups were not targeted,⁷⁵ although there is mounting evidence that using communication technologies may increase vaccine rates.⁷⁶

CONCLUSION

In high-income countries, unlike cervical cancer, there is no reliable and cost-effective screening method to prevent cancers attributed to HPV in men. In many LMICs, screening methods are not available for any cancer for either gender.⁷⁷ In addition, in LMICs, higher incidence of certain male cancers, lack of effective treatment, high prevalence of HIV, and attitudes towards sexual orientation, all support a universal vaccination strategy.

Universal vaccination of all young, adolescent women, and with available resources at least for high-risk groups of men, should be a global health priority. Development of multi-purpose STI vaccines for, for

example, Hepatitis A and B and HPV should also be considered. Political leaders, healthcare providers and public health officials in LMICs need to take challenging and sometimes politically contentious decisions to “prevent the preventable”. The pharmaceutical industry also should play their part, providing affordable ways in which a universal HPV vaccination strategy can be realised, particularly in LMICs. Failure to do so will result in the continuation of avoidable cervical cancer deaths especially in LMICs (whereby 260,000 women die each year),⁷⁷ and thousands of men dying from other HPV-related cancers.⁵³

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